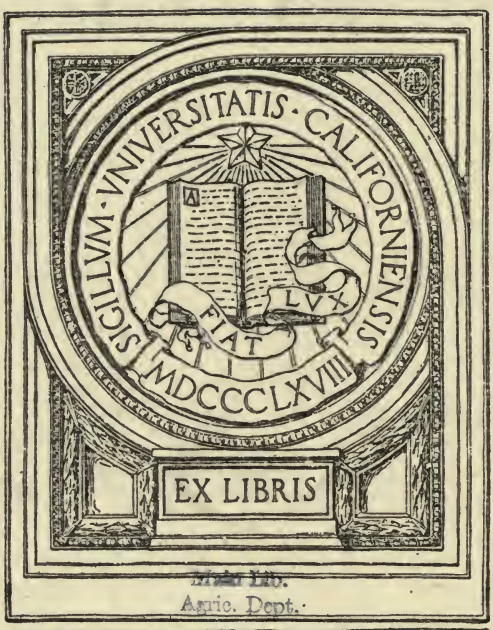

United States Department of Agriculture,

BUREAU OF CHEMISTRY—Circular No. 31.

H. W. WILEY, Chief of Bureau.

GENERAL RESULTS OF THE INVESTIGATIONS SHOWING THE EFFECT OF SALICYLIC ACID AND SALICYLATES UPON DIGESTION AND HEALTH.[a]

ORGANIZATION OF THE EXPERIMENT.

CONTROL OF SUBJECTS.

The experiments were conducted on twelve young men volunteers, chiefly from the Department of Agriculture, who voluntarily assumed the obligations imposed by work of this kind. They pledged themselves to abide by the rules and regulations guiding their conduct during the period of the observation, to indulge in no unusual exercise or study, to pursue the ordinary tenor of their daily lives without any more variation than is incident to regular habits. They further undertook to eat only the food which was given them at the hygienic table, to collect and deliver for analysis the excreta of their bodies, to observe regular hours respecting sleep and work, and to report the quantity of water which was drunk away from the hygienic table. The young men were not placed under surveillance, but simply were trusted with their pledge that they would not violate any of the rules of conduct prescribed.

THE RATION.

The work was conducted in a manner which has already been described,[b] namely, by first ascertaining in the fore period the quantity of food necessary to satisfy the ordinary demands of hunger and

[a] By reason of the restrictions placed upon the printing and distribution of the bulletins of the Department of Agriculture, it is not possible to supply the demand for Bulletin 84, Influence of Food Preservatives and Artificial Colors on Digestion and Health, from the regular edition. In order to meet this demand and to give as wide a circulation as possible to the results of the experimental work, it has been deemed advisable, in the case of Part II on Salicylic Acid and Salicylates, as with Part I, Boric Acid and Borax, to publish the general results in the form of a circular for more general distribution. In explanation of results obtained in this circular, attention is called to the fact that the methods pursued in the investigation were essentially those described in Bulletin 84, Part I, and in Circular 15, Results of Borax Experiment.

[b] Circular 15, Bureau of Chemistry, U. S. Dept. of Agriculture.

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preserve the body in a state of equilibrium. It was found that the amount of dry matter contained in the food consumed averaged a little less than 1 per cent of the weight of the body, the exact average for the whole experiment being 0.9 per cent. In other words, each healthy young man consumes each day an amount of dry food equivalent, approximately, to 1 per cent of the weight of his body. In the case of a man weighing 150 pounds, therefore, the amount of dry food consumed is about 1½ pounds daily. Including the moisture in the food and drink, the total quantity of food consumed by each young man is 4.2 per cent of his weight. Thus the total amount of food and drink consumed by an individual weighing 150 pounds is a little over 6 pounds daily. The diet was varied so as to give a choice of meats and vegetables, with bread, butter, milk, coffee, and tea. The best qualities of foods were purchased free of any added preservative or coloring matter and in a perfect state of preservation. The cooking was done in the Department of Agriculture, and every precaution was used to have the food and all the appurtenances of the table perfectly sanitary. While the kitchen and dining room were in the basement and perhaps might not be considered especially attractive, scrupulous neatness was observed.

ADMINISTRATION OF THE PRESERVATIVE.

The periods of observation were divided into groups of five days each, two periods being used for the preliminary or fore period, namely, ten days; six periods, or thirty days, for the administration of the preservative; and two periods, or ten days, for the after period. The salicylic acid was given in small and increasing doses, beginning with 0.2 gram, namely, 3 grains, and gradually increasing the dose to 2 grams, or 30 grains. The administration of the preservative extended in this case from October 29, 1903, to November 27, 1903, a period of thirty days. The preservative was administered in the two forms considered to be most convenient and most commonly used by physicians, namely, in tablets and in capsules. Objections have been urged against this manner of administering a preservative and it has even been stated in some of the criticisms of the borax experiment that the use of this method is sufficient ground for the rejection of all the data collected relative to the injurious effects of the preservative upon the metabolic processes. It is hardly necessary to call attention to the groundlessness of such an objection. In all medical and pharmacological work the materials which are used for study are given either in the food in the form of tablets or capsules, or injected directly into the blood. If, therefore, the data which have been collected in these experiments are to be rejected by reason of the method of administration, the whole mass of data based upon medical and pharmacological experimental work is to be

rejected for similar reasons. This criticism, therefore, is of the most preposterous character and shows to what extremes those who are dissatisfied with the results of these experiments may go in order to prejudice the public against their value.

EXAMINATIONS AND ANALYSES MADE.

Each one of the young men was carefully examined for organic or other troubles and no one was admitted to the table who was not perfectly sound physically and who had not been free from any serious illness for at least a year. As much or even greater care was exercised in this case than is given to the examination of candidates for life-insurance policies. Each young man was subjected to careful medical control during the entire period of the experiment in regard to his temperature, rate of pulsation, and character of any symptoms of disease of any kind which were developed. A daily record was made of this clinical and medical history, which was made the basis of a general discussion concerning these points. The weight and water content of the feces and the volume and specific gravity of the urine were determined each day, and these excreta were subjected to careful chemical analysis.

These analytical data, combined with the analytical data obtained for the food products, established the basis for the chemical study of the changes in the metabolic activities of the young men during the progress of the investigation. An elaborate study was also made of the sulfur occurring in the urine in regard to its distribution in different sulfur compounds and especially in relation to the content of nitrogen. Microscopic examinations of the urine were conducted at all periods for the purpose of ascertaining what influence, if any, the exhibition of salicylic acid had upon these bodies. In a similar manner a microscopic examination was made of the blood, including the estimation of the number of corpuscles, both red and white, contained therein. All possible precautions, in view of the magnitude of the work, were observed in securing a complete chemical and clinical control of each one of the young men engaged in the experimental work. By reason of illness and other unavoidable incidents only nine of the young men engaged in the work are admitted to the general comparison. The fragmentary and unsatisfactory data of the other three, while they are recorded, are not included in the general discussion. These data, however, are of a character which, had they been included in the general discussion, would not have altered the general conclusions derived therefrom. There can be no fault imputed to the final conclusions due to the exclusion of these fragmentary data. The results of the work are offered to the medical profession, to the officials in charge of National and State food control, and to the public with the hope that the

work will be carefully considered and that there will be accorded to it that measure of professional and public confidence which its character merits.

SUMMARY OF RESULTS.

CLINICAL AND MEDICAL DATA.

A study of the clinical and medical history of the men under observation indicates that the administration of the salicylic acid at first produces a stimulating effect upon the processes of solution and absorption of the food materials from the alimentary canal. There is a smaller proportion of the food products in the feces, both in the individual cases and as a whole, during the preservative period, and part of the after period is subject still to the effects of the administration of the preservative. There is also reported in the clinical and medical history an increased appetite in the case of the majority of the subjects. Altho the quantity of food which had been found sufficient for the normal functions of the body during the fore period is not diminished, and even to a slight extent in most instances increases, a feeling of hunger develops in almost every case, showing a disturbance of some kind in the metabolic process. The nature of this disturbance is disclosed in the chemical studies, while its observation is a prominent feature of the clinical and medical history. Judged by the development of hunger alone the administration of the salicylic acid might be considered a stimulant. When, however, all the functions of the body are in a normal state, there is no need of a stimulant, and the effect produced by the administration of the acid is evidently, therefore, an abnormal one. In cases where it is advisable to stimulate temporarily the digestive organs an effect such as that produced would be desirable if not continued too long. The physiological history of the use of stimulants, however, shows that they are temporary in their effects; that the increased activity produced by them is at the expense of the total vitality of the organ. Hence stimulants are indicated only for temporary or intermittent use. The truth of this statement is wholly established by the subsequent data gathered from the clinical and medical history of the subjects. The temporary hunger, while accompanied in a number of cases by heaviness and uneasiness in the epigastric region, does not cause any very great discomfort, and in the majority of cases the abnormal desire for food soon decreases. The same quantity or a slightly increased quantity of food is consumed thruout the administration of the preservative.

The loss of weight which is observed in almost all cases indicates that the apparent stimulation of the digestive process is not attended with any corresponding benefit in the building up of the tissues of the body. Assuming, as is done constantly in these

studies, that the energy developed by each individual remains practically constant, any increased absorption of food materials should have been followed by an increase in body weight. On the contrary, as is shown in the study of the balances, the katabolic activities are increased more strongly than the anabolic. There is a more vigorous tearing down of the tissues of the body than there is a building up thereof, and thus the observations made in the clinical and medical history are thoroly corroborated by the chemical studies of the foods and the products of metabolism. The general study of the medical data shows in some instances decidedly unfavorable symptoms attending the use of salicylic acid, while in a minority of cases no unfavorable symptoms of a diagnostic character are developed. After carefully weighing all the data favorable and unfavorable to the salicylic acid, disclosed in the detailed statement of the medical history, the conclusion is inevitable that taken as a whole the effects produced by its administration are unfavorable. It is true that there are individual cases which, taken alone, would lead presumably to a contrary opinion, and to these due weight is given in the general conclusion. As a jury considering conflicting testimony gives weight to that which seems most convincing and least open to doubt, so in the decision of this case from the medical history the verdict must follow the weight of testimony and be given against the defendant, namely, salicylic acid.

A summary of the most important indications leading to these conclusions is as follows, dealing with the average results obtained on body weight, effect on the blood and urine, and the metabolism of nitrogen and phosphoric acid:

THE WEIGHT OF THE BODY.

If all the variations in weight be taken as a whole for the nine men who completed the periods, it is noticed that there is a gradual diminution in weight, which falls from 62.71 kilograms with an average of 555 grams of dry food per day in the fore period to an average of 62.27 kilograms with an average of 564 grams of dry food per day in the preservative period. This loss of weight is continued in a more marked degree in the after period, where the average weight is 61.61 kilograms with 568 grams of dry food. Thus, altho the quantity of food is increased, the weight of the body is diminished. The general conclusion, therefore, in regard to the effect of the preservative upon the weight of the body is that there is a greater waste than there is a building up of the tissues, assuming, as we may practically do, that the amount of energy and the temperature remain reasonably constant. The general effect, therefore, of the salicylic acid is, under the conditions specified, to diminish the weight of the body; in other words, to interfere with the processes

of nutrition by exciting the katabolic activities to a greater degree than the anabolic.

THE MICROSCOPIC BODIES IN THE BLOOD.

There is an increase in the number of red corpuscles in the blood and also a slight increase in the number of white corpuscles during the period of the administration of the preservative. The intensity of the color of the blood diminishes, however, both in the preservative and in the after period. There is a marked decrease in the number both of red and white corpuscles in the after period. The apparent increase, therefore, in the preservative period is followed by a very considerable decrease in the after period. No conclusion, favorable or unfavorable, can be drawn from this observation regarding the use of the preservative, tho apparently, if there is any effect produced, it should be attributed to a favorable influence of the preservative in increasing the number of red corpuscles.

INFLUENCE OF THE PRESERVATIVE UPON THE URINE.

VOLUME.

But little influence of the salicylic acid on the volume of the urine is noticed. The average quantity of urine excreted per day is very slightly larger in the preservative period than in the fore period, for the nine men taken together, while in the after period it is slightly less. There is, therefore, a very slight tendency manifested, which is of no particular significance, to increase the volume of the urine. There is also noticed a slight increase in the total solids excreted in the urine, and this increase is maintained in the after period. This observation is in harmony with that indicated by many of the other phenomena which show that the salicylic acid has increased the katabolic activities of the body.

PRESENCE OF ALBUMIN.

In so far as the limited observations made on this point in the main experiment on the twelve men are concerned, the administration of the salicylic acid did not produce any notable effect upon the occurrence of albumin in the urine. In the special study made subsequently of four men, a marked tendency is shown to increase the occurrence of albumin.

MICROSCOPIC BODIES.

The occurrence of microscopic bodies in the urine is a normal condition, and therefore the only point which can be considered here is to determine whether or not the exhibition of the salicylic acid tended to increase or diminish their number. The mass data collected for the nine men indicate that there was a tendency on the part of the salicylic acid to increase the number of microscopic bodies in the urine,

the average relative occurrence rising from 68.3 per cent in the fore period to 78.3 per cent in the preservative period, and showing still an additional rise to 79.4 per cent in the after period. Inasmuch as most of the microscopic bodies are considered to be more or less associated with the katabolic products of the body, their increase tends to confirm the supposition already entertained, namely, that the salicylic acid has a greater influence upon the destruction of the tissues of the body than it has upon their restoration. To this extent the increased appearance of microscopic bodies is to be regarded as an unfavorable indication.

EXCRETION OF THE SALICYLIC ACID.

As in most of the cases where an additional and extraneous substance is added to a food product, the kidneys are called upon to bear the principal effort of excretion. In the case of salicylic acid a large part of it is excreted unchanged in the urine. Other portions undergo changes of a more or less definite nature, and these changed products are also excreted to a large extent by the kidneys, and thus the burden of their work is increased. It is evident, therefore, that the exhibition of the salicylic acid tends to increase the burden which is placed upon the kidneys as the principal excretory organ of the body. Every increase of a burden of this kind must tend to shorten the period of activity of this organ and thus produce a deleterious effect. This is shown therefore to be the case in this instance, and for this reason it may be fairly supposed that salicylic acid is a deleterious substance, in that it increases the amount of work demanded of the kidneys.

THE EXCRETION OF NITROGEN.

The data collected in the experiment on twelve men show that the general effect of the salicylic acid is to increase slightly the quantity of metabolized nitrogen excreted by the kidneys, while the quantity of nonmetabolized nitrogen excreted in the feces is slightly decreased, resulting in a small decrease in the total percentage of nitrogen eliminated. The balance is somewhat greater in the preservative period, altho the amount of nitrogen ingested is slightly decreased. In the special study made of four men, two cases showed an increased excretion of metabolized nitrogen and two a decrease in the preservative period, indicating an inhibiting effect by the general average. These data as a whole indicate that the preservative tended to increase slightly the digestibility and absorption of the nitrogen ingested.

THE EXCRETION OF PHOSPHORIC ACID.

While in the case of nitrogen the general tendency of the salicylic acid is to increase the quantity of metabolized nitrogen excreted, just the contrary effect is shown in respect of the phosphoric acid.

There is a well-developed tendency during the administration of the salicylic acid to increase the store of phosphoric acid in the body, since the amount absorbed from the alimentary canal is slightly increased and the quantity excreted by the kidneys is decreased. It is evident, therefore, that there is a storing of phosphatic material in the tissues due to the effect of salicylic acid. It is doubtful if such an increased store would prove of any lasting benefit in its effects, nor would it be just to claim that it would be injurious. The most that can be said in this case is that there is a decided disturbance of phosphoric acid metabolism in the direction of increasing the stores of phosphorus in the body, while in the case of nitrogen there is no marked effect produced on the metabolic process.

THE USE OF SMALL QUANTITIES OF THE PRESERVATIVE.

The arguments which have been advanced in excuse of the use of preservatives when used in minute quantities have perhaps been more vigorously urged for salicylic acid than for almost any other substance. Since the publication of Part I of Bulletin 84 this argument has been urged with such vigor and such ingenuity that a further reference may not be out of place in these general conclusions. The principle which is laid down is that a substance which is injurious to health when added to foods, if not a natural constituent thereof, or if not added for condimental purposes, does not lose its power of injury to health because it is diluted or given in small quantities. The only change which is made is to mask the injurious effects produced—to make them more difficult of ascertainment and impossible of measurement. This subject was fully discust in the hearings before the House Committee on Interstate and Foreign Commerce in February, 1906. The fallacy of the argument that small quantities of an injurious substance are not injurious may perhaps be best represented graphically. The chart which accompanies this discussion shows theoretically the normal and lethal dose of a food and a drug or, as in this case, a chemical preservative. The chart shows two curves, one representing a chemical preservative and one representing a food. The normal dose of a food is that quantity of food which maintains a healthy adult body in equilibrium. It is represented in the chart on the right by the number 100. If the quantity of food necessary to maintain the equilibrium in a healthy adult body is slightly diminished, no apparent change is at first experienced and possibly even no discomfort. If, however, the quantity of food be still further diminished progressively, as indicated by following the curve down to the left, the point is finally reached when no food is given at all and death ensues, represented by 0 on the left hand of the diagram designated "Lethal dose." As the curve begins to deviate from the perpen-

dicular on the right the degree of injury is very readily noticed and starvation or symptoms of starvation are set up. Thus if you follow the perpendicular on the right downward to the point 80 the divergence of the corresponding point of the curve is already measurable. As you descend to 0 the magnitude of the measurement increases. It requires but very little further illustration to show how easily the effect of diminishing the normal dose of a food can be measured immediately after the curve begins to vary appreciably from the perpendicular on the right.

Let us now consider the perpendicular on the left, which is marked at the top under the term "Lethal dose," namely, a quantity of the added preservative sufficient to destroy life. The normal dose of such an added chemical preservative is 0 and is shown at the base line to the right, marked "Normal dose." If you add a very minute quantity of a chemical preservative, the curve representing it varies so slightly from the horizontal base as to be impossible of measurement by ordinary means. If we follow along to the number 75 on the horizontal base we see the deviation of the curve is sufficiently great to measure. At 50 it is still greater, at 25 still greater, while at the left of the basic line it is a maximum extending from 0 to 100, or the lethal dose. It is easy to show by mathematical data that no matter how small the quantity of an injurious substance or preservative it will still produce an injurious effect which may be infinitely small if the dose be infinitely small. It follows, then, as a mathematical demonstration that any quantity of an injurious substance added to a food product must of necessity be injurious, provided it is in the nature of a drug and the body is in a perfectly healthy, normal condition.

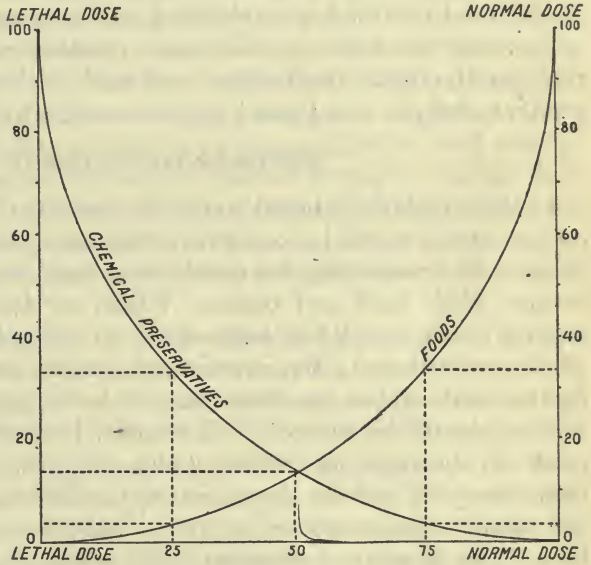

FIG. 1.—Graphic chart representing the comparative influences of foods and preservatives.

Hence the argument which has been so persistently urged in favor of a chemical preservative, that if in small quantities it is harmless, is shown to be wholly untenable. While there is no necessity for

the addition of a harmful substance, where no particular benefit is secured thereby, and where there is no disturbance of the normal state of health, there can be no possible excuse of a valid nature to offer for the exhibition of even minute quantities. That these minute quantities would not be dangerous in so far as producing any fatal effect is concerned is conceded, but that in the end they do not produce an injury even in these small quantities is certainly to be denied. The course of safety, therefore, in all these cases is to guard the opening of the door. If the admission of small quantities is permitted, then there can never be any agreement among experts or others respecting the magnitude of the small quantity, and continued litigation and disagreement must follow. On the other hand, when the harmfulness of any substance which it is proposed to add to food is established and no reason for its use can be given other than the convenience, carelessness, or indifference of the manufacturer, the exclusion of such bodies entirely from food products follows as a logical sequence and a hygienic necessity.

GENERAL CONCLUSIONS.

In the conclusions based upon the general observations the same conservatism must be observed, together with the same general reservations respecting the conclusions that are found in Part I concerning boric acid and borax. While, as described in the borax report, the attempt has been made to control, as far as possible, all the conditions of the experimental work, the difficulties attending the task are so enormous that it is not possible that complete success should be secured. There has, however, been no attempt made to discriminate in the choice of data, all the observations being recorded and the discussion of the individual data based upon the tabular statements being given without prejudice and without bias. The general assumption has been made, as in the previous case, that by reason of the regular habits of life which were imposed upon the subjects the amount of energy developed and the quantity of nourishment expended therein are reasonably constant thruout the experimental period. If these factors vary, as they necessarily must to a certain degree, it is evident that they vary uniformly above or below the average, and hence these variations could not possibly produce any notable effect upon the final result.

There has been a general consensus of opinion among scientific men, including the medical profession, that salicylic acid and its compounds are very harmful substances, and the prejudice against this particular form of preservative is perhaps greater than against any other material used for preserving foods. This is due not only to the belief in the injurious character of salicylic acid, but perhaps is especially due to the fact that it has in the past been so generally used as an antiseptic.

That salicylic acid should be singled out especially for condemnation among preservatives does not seem to be justified by the data which are presented and discust in this bulletin. That it is a harmful substance, however, seems to be well established by the data taken as a whole, but it appears to be a harmful substance of less virulence than has been generally supposed. There is no doubt of the fact that salicylic acid is a drug which is often indicated in diseases well established, and also perhaps in certain conditions which, while verging on disease, might still be regarded as a state of health. But the administration of salicylic acid as a medicine should be controlled exclusively by the medical profession, and, while it is a remedy well established in the Pharmacopœia and especially prized for its effect upon rheumatism and gout, it does not seem that there should be any warrant in this fact for its promiscuous use in foods, even if it were harmless.

The data show very clearly that salicylic acid and salicylates appear to exert an exciting influence upon the activities which take place in the alimentary canal, stimulating the organs to greater effort, and this stimulation leads at first to increased digestion and absorption of the foods which are introduced into the stomach. In the light of the data which are exhibited salicylic acid may be said to increase the solubility and absorption of the food in the alimentary canal, so that larger parts of the nutrients taken into the stomach actually enter the circulation.

The data which show the effects just noted also indicate that the general effect upon the system is depressing, in that the tissues are broken down more rapidly than they are built up, and thus the normal metabolic processes are interfered with in a harmful way. The administration of the salicylic acid is attended by a gradual decrease in the weight of the subjects, altho the quantity of food elements administered during the preservative and after periods is slightly increased, which fact, together with a greater degree of absorption of the food elements, should have resulted in a slight increase in weight. This increase in weight, however, does not occur, and the disturbing influences of the salicylic acid upon metabolism, altho not very great, are specifically demonstrated.

The final conclusion in this matter, therefore, is that the unenviable position which salicylic acid has heretofore held among preservatives, in being regarded as the most injurious of all, is perhaps to a certain extent undeserved. Like other ordinary preservatives, it is not one which can be classed as a poison in the usual sense of the word. When used as a medicine in many cases of derangement of health it is, like the other chemical preservatives, often highly beneficial when properly prescribed by a competent physician. It is, when used in the food, at first an apparent stimulant, increasing the solubility and absorption of the common food elements from the alimentary canal.

It soon, however, loses its stimulating properties and becomes a depressant, tending to break down the tissues of the body more rapidly than they are built up. It disturbs the metabolic processes, in most cases producing conditions which are not normal and which apparently are not beneficial. It has a tendency to diminish the weight of the body and to produce a feeling of discomfort and *malaise* which, while not marked, is distinctly indicative of injury. In some cases these symptoms of *malaise* approach illness, and while not always diagnostic are sufficiently common to unmistakably point to the salicylic acid as their origin. It places upon the excretory organs, especially the kidneys, an additional burden which they are not able to bear and which can not possibly result in any good, but on the contrary must necessarily, by thus increasing the burden of the kidneys, finally result in injury, tho perhaps with the use of very small quantities of the preservative these organs would continue to perform their functions for many years before finally breaking down.

This work is offered as an unbiased study of all the data recorded, both of those which appear to be in favor of the use of salicylic acid and those which appear to be against its use, and leads to the inevitable conclusion that salicylic acid is a substance which, when added to foods even in small quantities, exerts a depressing and harmful influence upon the digestion and health and the general metabolic activities of the body. Further, there appears to be no necessity for its use, as food can be preserved in unobjectionable ways without its aid. Its indiscriminate use would tend to carelessness in the quantities employed, thus increasing the dangers to which the consumer is subjected. Also its use in the preservation of foods tends to induce carelessness and indifference on the part of the manufacturer, as when a chemical antiseptic is employed many of the processes necessary to the proper selection, cleaning, and preservation of foods may be omitted. The addition of salicylic acid and salicylates to foods is therefore a process which is reprehensible in every respect and leads to injury to the consumer, which, tho in many cases not easily measured, must finally be productive of great harm.

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Approved:
James Wilson,
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